EXHIBIT A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,293	04/01/2004	Paul Stark	54684C1	6126

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
11/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,293	STARK ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicants' Amendments and Remarks filed 14 July 2008. The Examiner acknowledges the following:

Claims 1, 6, 22 and 26-32 have been amended with clearly provided support.

The Examiner thus acknowledges that no new matter has been added.

No claims have been cancelled and no further claims have been added.

Thus, claims 1-32 still represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statement (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Objection to the Claims

Applicants' remarks regarding claim 4 and editorial amendments to claims 6 and 22, render moot the objections to claims 4, 6, and 22. Thus, said objections have been **withdrawn**.

Rejections under 35 USC 112

Applicants' amendments and remarks to claims 26-32 render moot the new matter rejection to claims 26-32, under 35 USC 112, first paragraph. Thus, said rejection has been **withdrawn**.

Applicants' amendments and remarks to claims 26-32 render moot the new matter rejection to claims 26-32, under 35 USC 112, first paragraph. Thus, said rejection has been **withdrawn**.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Action dated 12 March 2008:

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda et al. (U.S. Patent 5,137,733) in view of Oshlack et al. (U.S. Patent 5,580,578).

The instant claims 1, 2, 26, 27 and 30 are drawn to a multiparticulate bisoprolol formulation wherein each particle comprises a core of bisoprolol or a pharmaceutically acceptable bisoprolol salt surrounded by a release-controlling, polymeric coating. Claims 3 and 28 further limit the drug to a pharmaceutically acceptable salt of bisoprolol (e.g. bisoprolol fumarate or hemifumarate). Dependent claims 4 and 29 further limit the bisoprolol salt of claim 3 to bisoprolol hemifumarate. Claims 5 and 6 recite *in vitro* release profile limitations to the formulation. Claims 7 and 8 further limit the composition of claim 1 such that a sealant is applied to the medicated core prior to application of the polymeric coating. Claim 9 further limits the formulation such that the bisoprolol active ingredient is applied to a core particle (e.g. non-pareil seed) having an average diameter between 400 and 1100 microns. Claims 10 and 11 further limit the polymeric coating of claim 1 wherein the polymer of claim 10 is a major proportion of the coating with low permeability and claim 11 is a minor proportion of the coating with high permeability. Claim 12 further limits the coating of claim 10 such the at least one of polymers is a methacrylic acid copolymer. Claim 13 further limits the coating of claim 10 such the at least one of polymers is a ammonio methacrylate copolymer. Claim 14 further limits the polymer coating of claim 12 such that a mixture of polymers is used. Dependent claim 15 further limits the polymer coating by including one or more soluble excipients. The soluble excipients are further limited by category in (e.g. soluble polymer, surfactant, etc.) in claim 16 and by compound (e.g. PVP, PEG, and mannitol) in claim 17. Claim 18 further limits the soluble excipient of claim 15 such that the excipient is present between 1-10% by weight based on the total dry weight of the polymer. Claim 19 recites the addition of one or more auxiliary agents to the polymer coating. Claims 20 and 21 further limit the formulation of claim 1, such

that the polymer coating contributes to the overall formulation, a given weight percentage of the core. Claim 20 recites a 10-100% weight gain on the core whereas claim 21 recites a 25-70% contribution. Claim 22 further limits the formulation of claim 1 (see Claim Objections above), such that a sealant is applied to the polymeric coating. Claim 23 recites useable examples for said sealant. Claim 24 recites different oral dosage forms that may encompass the bisoprolol formulation. Claim 25 further limits the type of tablet form of the formulation (e.g. disintegrating, effervescent, etc.). Claims 31 and 32 further limit the composition of claim 26 to particular amounts of bisoprolol.

Noda teaches a controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellant salt and a water-insoluble and slightly water-permeable acrylic polymer having a methacrylic copolymer group (claim 1). Example 12 teaches the medicinal agent to be bisoprolol fumarate. Noda also teaches that the system is designed to have an initial lag period before the medicinal agent is released or dissolved and that this initial period can be varied depending upon the number of coating layers applied to the cores (col. 5, lines 19-56). Further, the preparation can retain an effective blood concentration for many hours and can again differ with the amount of layers applied to the cores (col. 5, lines 19-56). The preparation is suitable for a once-a-day administration (col. 6, lines 1-2). The website: http://pharmacycode.com teaches that the hemifumarate salt and fumarate salt have the same formula and structures. Non-pareil seeds (e.g. spherical particles) are taught to have a mean diameter between 500 and 1000 microns (col. 3, lines 16-18). Fillers, as defined by applicant (pg. 14, lines 13-14), include magnesium stearate and calcium stearate, both of which Noda teaches in claim 1 as being part of the coating. An

additional coating layer is added to the cores after the acrylic polymer layer (col. 2, lines 32-39). The acrylic polymers are taught at col. 2, lines 40-59 and include Eudragit RS as well as a combination of Eudragit RS and RL. Example 6 teaches a coating layer with the Eudragit RS/RL combination. The additional coating layer is chosen from compounds such as hydroxypropyl cellulose (col. 2, lines 60-66). The amount of coating layer is about 5% to about 80% based on the weight of the core (col. 3, lines 11-21). Various excipients such as polyvinylpyrrolidone and mannitol are present in the core (col. 3, lines 37-57). The acrylic coating layer is further taught to comprise plasticizers (col. 4, lines 43-55). Still further, Noda teaches formulations with differing number of coating layers wherein the lag time and complete dissolution are different. Preparation (b) of Figure 1, prepared as polymer coated granular tablets in Test Example 1, exemplifies the dissolution profile of the instant claims.

While Noda teaches many of the limitations of the instant claims, the exact composition of the instant claims is not exemplified in the reference. That which is not expressly taught by Noda includes: application of the sealant is to the core prior to the application of the polymeric coating, the percent soluble excipient used (e.g. 1-10%), the percent weight contributions to the overall composition by the polymeric coating, and the amount of bisoprolol added to the composition.

Oshlack et al. teaches a controlled release formulation wherein a barrier layer is incorporated between the medicinal core and the acrylic coating layer (col. 13, line 62 to col. 14, line 2). The barrier layer can be hydroxypropyl methylcellulose or any film-forming agent known in the art (col. 13, line 62 to col. 14, line 2). Eudragit RS/RL dispersions mixed together in the desired ratios are taught as the polymer coatings (col. 9, lines 47-54).

In view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to prepare a controlled release system comprising bisoprolol fumarate in a core coated first, by a barrier layer and second by an acrylic polymer with a reasonable expectation of successfully obtaining the desired dissolution pattern of the drug from the dosage. Oshlack et al. teach that it may be desirable to obtain the desired efficacy by utilizing different coating components to effect an overall release of the active agent within the desired levels over a longer period of time (col. 18, lines 3-11). Therefore, modification of the instant dosage formulation to apply the barrier layer (e.g. hydroxypropyl methylcellulose) prior to applying the polymeric coating, as earlier defined, is well within the purview of the skilled artisan.

Furthermore, it is *prima facie* obvious to switch the order of addition of said barrier and polymeric layer(s) to the formulation with the result being that of the controlled release composition of Applicant's instant claims 1-32. The basis for this *prima facie* obviousness rejection can be found in the following case law: *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), wherein selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results; and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930), wherein selection of any order of mixing ingredients is *prima facie* obvious.

Neither reference teaches the percentage of soluble excipient included in the polymeric coating (e.g. 1-10%), the percent weight gain of the formulation contributed by the polymeric coating (e.g. 10-100% and 25-70%) or the amount of bisoprolol added to the formulation (claims 31 and 32) as claimed by the Applicants. Since the value of each parameter with respect to the claimed dosage form is adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a

routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of bisoprolol to add to the dosage formulation as well as the optimal percentages of coating and excipient to include in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these ingredient amounts would have been obvious at the time of Applicant's invention.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of clams 1-32 under 103 over Noda in view of Oshlack have been fully considered but they are not persuasive.

Applicants argue that the instantly claimed composition is one which is "specifically formulated to exhibit a release of bisoprolol that is affected by the pH of the medium" into which it is placed. Applicants further maintain that the skilled artisan could not predict from Noda that "employing pH-dependent polymers, as presently claimed, would show comparable delays *in vitro* and *in vivo*".

In response to Applicants' argument that the references fail to show certain features of Applicants' invention, it is noted that the features upon which applicant relies (i.e., *in vitro* dissolution versus *in vivo* dissolution) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With regard to the limitations recited in claims 5 and 6, which state release limitations for the active bisoprolol based on *in vitro* USP assay experimentation; until some material differences in the

properties of the claimed composition are demonstrated distinguishing it from that which is taught in the art, said functional limitations are considered by the Examiner to be directed toward the instantly claimed coated bisoprolol formulation recited in claim 1. Furthermore, Applicants' instantly amended claims do not recite a "specific formulat[ion]", particularly in view of amended claims 1 and 31-32, which respectively recite a broad list of enteric polymers of which one or more may be used, and as well as different amounts of bisoprolol which may be incorporated into the composition. Regarding the presently amended claim 1, Applicants' have added the limitation of a Eudragit polyacrylic acid as further definition for the enteric polymeric coating. The Examiner respectfully submits that the amendment does not serve to distinguish the presently claimed composition from that which is taught in the art. Rather, as discussed in the previous action, Noda teaches the use of several different polyacrylic acids which include Eudragit RS and RL. In view of the teachings of the manufacturer's website (e.g. Evonik, formerly Degussa), both Eudragit RS and RL are copolymers formed of acrylates and methacrylates, thus making them formulations of polyacrylic acids which are expressly taught by Noda as being used for the purposes which are instantly claimed.

For these reasons and those already made of record, Applicants' arguments are found unpersuasive. Said rejection is therefore maintained.

NEW REJECTIONS

In light of Applicants' amendments, most notably to claim 1, the following rejections have been newly added:

CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation "Eudragit poly acrylic acid", and the claim also recites "Eudragit S and Eudragit L" which are narrower statements of the range/limitation.

Claim 1 contains the trademark/trade name "Eudragit®". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte*

Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe: poly acrylic acid, L-, and S-type polyacrylic compounds and, accordingly, the identification/description is indefinite.

All claims have been rejected; no claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615

Notice of References Cited	Application/Control No. 10/814,293	Applicant(s)/Patent Under Reexamination STARK ET AL.	
	Examiner Jeffrey T. Palenik	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,137,733	08-1992	Noda et al.	424/497
*	B	US-5,580,578	12-1996	Oshlack et al.	424/468
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	http://www.pharma-polymere.de/pharmapolymers/en/eudragit/sustainedreleaseformulations/
	V	http://www.pharma-polymere.de/pharmapolymers/en/eudragit/entericcoatings/
*	W	http://pharmacycode.com; for hemifumarate versus fumarate salt
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.